REMARKS

The undersigned would like to thank Examiners Gollamandi and Evans for the courteous and helpful interview on November 14, 2001.

Claims 33, 42-44, 46 and 48 have been amended and claims 56-88 have been added. These claims are supported by the original claims throughout the specification and no new matter is introduced.

Original claims 1-11 were directed to a sustained release formulation and claims 12-32 were directed to a modified release formation having both immediate and sustained release properties. New claims 33-88 are directed to the modified release formulation of original claims 12-32, while the sustained release claims have been canceled to facilitate prosecution without prejudice to Applicants' ability to pursue them separately in a continuation application. No new matter is believed to be introduced by this amendment. The upper limit in newly added claim 33 of about 6.8:1 for the ratio of hydrophilic polymer of water-insoluble polymer is supported by the specification at page 11, lines 23-25, which shows a preferred embodiment with a weight ratio that calculates to be 6.8:1 including the hydrophilic polymer in the guaifenesin DC. The range of values in newly added claim 43 for the ratio of first and second portions of guaifenesin is supported by the specification, see Examples 4 and 5. The ranges of component weight percents in newly added claim 55 are supported by the specification as they represent the ranges demonstrated by the Examples including the subcomponents of "guaifenesin DC" as defined in the specification at page 11, lines 8-9.

Original claims 1-32 were rejected under 35 U.S.C. § 103(a) as unpatentable over Drost et al., U.S. Patent No. 4,756,911, in view of Dansereau et al., U.S. Patent No. 5,032,406. To the extent that the Examiner has applied these references to original claims 12-32 and to the extent arguably applicable to newly added claims 33-88, Applicants respectfully traverse this rejection.

Drost et al. does not teach or suggest the invention as presently claimed. Drost et al. does not disclose a pharmaceutical composition containing guaifenesin or its therapeutic category, which is expectorant -- not bronchodialator. Drost et al. does not disclose a composition having both an immediate release portion that is fully bioavailable in the subject's stomach and a sustained release portion that provides therapeutically effective bioavailability for

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at least 12 hours. Moreover, Drost et al. does not disclose or suggest the use of a water-insoluble polymer, e.g., an acrylic resin, in such a modified release tablet.

Dansereau et al. does not supply the deficiencies of Drost et al. While Dansereau et al. does disclose two separate guaifenesin portions with different release characteristics, this disclosure describes a dual-action tablet that includes an outer portion that slowly releases a first dose of the drug and an inner portion that provides a second dose which is delayed until some time after administration, i.e., until the outer portion is dissolved sufficiently to expose the inner portion to gastric fluids. Such an approach is totally different from that of the claimed invention.

The Dansereau et al approach does not provide the unexpected advantages of the present invention. The modified release product of the present invention combines a short T_{max} that results from the immediate release portion with a C_{max} that is sufficiently higher to give early symptomatic relief through providing expectorant activity above the minimum effective treatment threshold. Immediate release only formulation have this high C_{max} because of the rapid fall-off of concentration due to short half life of guaifenesin. Getting above the minimum effective concentration threshold early in the dosing regimen is more effective in getting symptoms under control and, has the added advantage in the dual acting formulation of the present invention that not as much drug is needed thereafter to maintain the symptomatic control. The Dansereau approach however, employs its protected inner immediate release portion as a delayed bolus that merely is intended to keep the end of the profile up to minimum effective concentration because absorption in the lower gastrointestinal tract is not as good at lower concentrations. This approach does not provide the early T_{max} or the higher C_{max} achievable with the present invention. In fact, Dansereau et al. specifically teaches away from employing any immediate release portion: "This dual-action tablet is contrasted with repeat-action tablets which give an immediate dose followed by a sustained dose" (col. 2, lines 37-39) (emphasis added). This general statement by Dansereau that repeat-action formulations exist does not provide any specific teaching with respect to guaifenesin products and does not provide any suggestion that guaifenesin should be formulated as a "repeat-action" tablet. Moreover, the inner dose of Dansereau et al. is not "fully bioavailable in the subject's stomach" because of the time delay caused by the slow-release outer portion.

The Examiner has not pointed to any suggestion in the references cited or the art to combine the teachings of Drost et al. and Dansereau et al. In fact, these references present alternative approaches to providing long acting drug administration and as such would not be

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combined. Even if it were proper to combine the teachings of Drost et al. and Dansereau et al., the resulting combination would not disclose or suggest the claimed invention. At best, such a combination would suggest only that Dansereau et al.'s outer portion might employ the release chemistry of Drost et al.'s composition. This combination falls woefully short of suggesting the claimed invention since it is still "inside out" from a functional standpoint, i.e., has no immediate release portion.

Respectfully submitted,

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APPENDIX A

VERSION OF CLAIMS WITH MARKINGS

Please amend claims 33, 42-44, 46 and 48 and add new claims 56-88, which are provided in a marked version format in accordance with 37 C.F.R. § 1.121(b) as follows:

33. A modified release tablet having two portions, wherein a first portion comprises a first quantity of guaifenesin in an immediate release form which becomes fully bioavailable in the subject's stomach and a second portion comprises a second quantity of guaifenesin and a release-delaying matrix comprising a hydrophilic polymer and a water-insoluble polymer wherein the weight ratio of said hydrophilic polymer to said water-insoluble polymer is in the range of from about 1:1 to about 6.8:1, wherein said tablet demonstrates a C_{max} in a human subject equivalent to [an immediate release guaifenesin product] the C_{max} obtained when the first of three doses of a standard immediate release formulation having one third the amount of guaifenesin is dosed every four hours over a 12 hour period, and wherein said tablet also provides therapeutically effective bioavailability for at least twelve hours after [dosing] a single dose in a human subject according to serum analysis.

42. The modified release tablet of claim [39] 33 wherein the C_{max}, AUC_{inf} and AUC_{0-12} are approximately proportional to dosage strength.

43. The modified release tablet of claim 33 or 39 wherein the ratio of said first quantity of guaifenesin to said second quantity of guaifenesin is about 1:1 to about [5:1] 1:5.

44. The modified release tablet of claim 33 or 39 wherein the ratio of said first quantity of guaifenesin to said quantity of second quantity of guaifenesin is about [5:1] 1:5.

46. The modified release tablet of claim [44] 41 wherein the C_{max} of said tablet is at least 1900 μg/mL and said tablet has an AUC_{inf} of at least 7000 hr*μg/mL.

48. The modified release tablet of claim [47] 40 wherein the C_{max} of said tablet is at least 1000 μg/mL and said tablet has an AUC_{inf} of at least 3500 hr*μg/mL.

--56. A modified release product having two portions, wherein a first portion comprises a first quantity of guaifenesin in an immediate release form which becomes fully bioavailable in the subject's stomach and a second portion comprises a second quantity of guaifenesin in a sustained release form wherein the ratio of said first quantity to said second quantity provides a C_{max} in a human subject equivalent to the C_{max} obtained when the first of three doses of a standard immediate release formulation having one third the amount of guaifenesin is dosed

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every four hours over a 12 hour period and wherein said product also provides therapeutically effective bioavailability for at least twelve hours after a single dose in a human subject according to serum analysis.

57. The modified release product of claim 56 wherein the total quantity of guaifenesin is from about 600 mg to about 1200 mg.

58. The modified release product of claim 56 wherein the total quantity of guaifenesin is 600 mg.

59. The modified release product of claim 56 wherein the total quantity of guaifenesin is 1200 mg.

60. The modified release product of claim 56 wherein the C_{max}, AUC_{inf} and AUC_{0-12} are approximately proportional to dosage strength.

61. The modified release product of claim 56 or 57 wherein the ratio of said first quantity of guaifenesin to said quantity of second quantity of guaifenesin is about 1:1 to about 1:5.

62. The modified release product of claim 61 wherein the ratio of said first quantity of guaifenesin to said quantity of second quantity of guaifenesin is about 1:5.

63. The modified release product of claim 59 wherein the C_{max} of said product is from about 1600 to 2500 μg/mL and said product has an AUC_{inf} of from about 5600 to 8750 hr*μg/mL.

64. The modified release product of claim 59 wherein the C_{max} of said product is at least 1900 μg/mL and said product has an AUC_{inf} of at least 7000 hr*μg/mL.

65. The modified release product of claim 58 wherein the C_{max} of said product is from about 800 to 1250 μg/mL and said product has an AUC_{inf} of from about 2800 to 4375 hr*μg/mL.

66. The modified release product of claim 58 wherein the C_{max} of said product is at least 1000 μg/mL and said product has an AUC_{inf} of at least 3500 hr*μg/mL.

67. The modified release product of claim 56 wherein said product has a half life, according to serum analysis, of at least three hours.

68. The modified release product of claim 56 wherein said first and second portions each comprise abutting substantially planar layers which form a bilayer tablet.

69. The modified release product of claim 56 wherein said first portion is provided as a coating on said second portion.

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70. The modified release product of claim 56 which is a capsule containing said first and second portions.

71. The modified release product of claim 56 which is approximately equally effective when administered to a patient on an empty or full stomach.

72. The modified release product of claim 59 which has the serum guaifenesin concentration profile of Figure 10.--

73. A modified release product having two portions, wherein a first portion comprises a first quantity of guaifenesin in an immediate release form which becomes fully bioavailable in the subject's stomach and a second portion comprises a second quantity of guaifenesin in a sustained release form wherein the ratio of said first quantity to said second quantity is from about 1:1 to about 1:5 and the product provides a C_{max} in a human subject equivalent to the C_{max} obtained when the first of three doses of a standard immediate release formulation having one third the amount of guaifenesin is dosed every four hours over a 12 hour period and wherein said product also provides therapeutically effective bioavailability for at least twelve hours after a single dose in a human subject according to serum analysis.

74. The modified release product of claim 73 wherein the total quantity of guaifenesin is from about 600 mg to about 1200 mg.

75. The modified release product of claim 73 wherein the total quantity of guaifenesin is 600 mg.

76. The modified release product of claim 73 wherein the total quantity of guaifenesin is 1200 mg.

77. The modified release product of claim 73 wherein the C_{max}, AUC_{inf} and AUC_{0-12} are approximately proportional to dosage strength.

78. The modified release product of claim 73 wherein the ratio of said first quantity of guaifenesin to said quantity of second quantity of guaifenesin is about 1:5.

79. The modified release product of claim 76 wherein the C_{max} of said product is from about 1600 to 2500 μg/mL and said product has an AUC_{inf} of from about 5600 to 8750 hr*μg/mL.

80. The modified release product of claim 76 wherein the C_{max} of said product is at least 1900 μg/mL and said product has an AUC_{inf} of at least 7000 hr*μg/mL.

81. The modified release product of claim 75 wherein the C_{max} of said product is from about 800 to 1250 μg/mL and said product has an AUC_{inf} of from about 2800 to 4375 hr*μg/mL.

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82. The modified release product of claim 75 wherein the C_{max} of said product is at least 1000 μg/mL and said product has an AUC_{inf} of at least 3500 hr*μg/mL.

83. The modified release product of claim 73 wherein said product has a half life, according to serum analysis, of at least three hours.

84. The modified release product of claim 73 wherein said first and second portions each comprise abutting substantially planar layers which form a bilayer tablet.

85. The modified release product of claim 73 wherein said first portion is provided as a coating on said second portion.

86. The modified release product of claim 73 which is a capsule containing said first and second portions.

87. The modified release product of claim 73 which is approximately equally effective when administered to a patient on an empty or full stomach.

88. The modified release product of claim 76 which has the serum guaifenesin concentration profile of Figure 10.